Amendments to the Specification

Please add a paragraph beginning at page 1, after the title with the following paragraph:

Cross Reference to Related Applications

This is a § 371 U.S. national stage of PCT/GB2004/002827, filed June 28, 2004, which was published in English under PCT Article 2(2), and claims the benefit of Great Britain application 0315182.6, filed June 28, 2003. Both applications are incorporated herein in their entirety.

Please replace the paragraph beginning at page 19, line 8, with the following rewritten paragraph:

Figure 1 shows the amino acid sequence of human GH (SEQ ID NO: 9) with binding site for GHR indicated with arrows;

Please replace the paragraph beginning at page 19, line 11 with the following rewritten paragraph:

Figure 2 shows the nucleic acid sequence of human GH (SEQ ID NO: 10);

Please replace the paragraph beginning at page 19, line 13 with the following rewritten paragraph:

Figure 3 shows the amino acid sequence of GHR (SEQ ID NO: 11) (extracellular domain underlined);

Please replace the paragraph beginning at page 19, line 15 with the following rewritten paragraph:

Figure 4 Cloning strategy for the circular permutation of Growth Hormone. In the first PCR reaction a forward primer (GH_CPFor (SEQ ID NO: 13)) and a linker primer (GH_CPLink (SEQ ID NO: 14)) are used to produce a 'megaprimer'. This megaprimer is used with a reverse primer (GH_CPRev (SEQ ID NO: 15)) to generate the circularly permutated GH gene. Appropriate restriction sites [BamHI (B) and NotI (N)] are engineered into the forward and reverse primers to facilitate ligation into the vector pTrcHis-TOPO;

Please replace the paragraph beginning at page 19, line 22 with the following rewritten paragraph:

Figure 5: Schematic and DNA sequence showing the strategy used to generate GH_CP01 (SEQ ID NO: 12). (A) a schematic diagram showing how GH is transformed into GH_CP01 (SEQ ID NO: 12); Glu120 (grey disc) is removed by initiating the new gene at residue 121 and terminating the protein at residue 118, the 'old' termini are linked by joining the termini to make a 6 amino acid linker. The helices are numbered in order (from N to C terminus) and the arrows denote the direction of the helices (from N to C). (B) the DNA sequence of GH and GH_CP01 (SEQ ID NO: 12); the nucleotides removed from GH to produce GH_CP01 (SEQ ID NO: 12) are underlined, the initiation nucleotide for GH_CP01 (SEQ ID NO: 12) in GH, and *vice versa*, are shown in bold;

Please replace the paragraph beginning at page 20, line 16 with the following rewritten paragraph:

Table 1 Primers used to generate GH_CP01 (GH_CP01For (SEQ ID NO: 13), GH_CP01Rev (SEQ ID NO: 15)). The bold characters denote sequence which anneals to the GH gene; the underlined characters denote endonuclease restriction sites (BamHI – ggatcc; NotI – gcggccgc). In the linker primer, GH_CP01Link (SEQ ID NO: 14), the sequence which anneals to the carboxy terminus of GH is shown in UPPER-CASE.

Please replace the paragraph beginning at page 20, line 22 with the following rewritten paragraph:

Table 2 Primers used to generate further circularly permuted GH molecules. GHPermL01+ is put forth as SEQ ID NO: 16, GHPermL01- is put forth as SEQ ID NO: 17 GHPermN01+ is put forth

<u>as SEQ ID NO: 18 GHPermC01- is put forth as SEQ ID NO: 19 GHPermN01+ is put forth as SEQ ID NO: 20 GHPermC02- is put forth as SEQ ID NO: 21 GHPermN01+ is put forth as SEQ ID NO: 22 GHPermN04+ is put forth as SEQ ID NO: 24 GHPermC01- is put forth as SEQ ID NO: 25 GHPermN04+ is put forth as SEQ ID NO: 26, GHPermC02- is put forth as SEQ ID NO: 27, GHPermN06+ is put forth as SEQ ID NO: 28, GHPermC06- is put forth as SEQ ID NO: 29, GHPermN07+ is put forth as SEQ ID NO: 30, GHPermC07- is put forth as SEQ ID NO: 31.</u>

Please replace the paragraph beginning at page 24, line 3 with the following rewritten paragraph:

```
IQTLMGRLED  GSPRTGQIFK  QTYSKFDTNS  HNDDALLKNY  GLLYCFRKDM  DKVETFLRIV
QCRSVEGSTI  PLSRLFDNAS  LRAHRLHQLA  FDTYQEFEEA  YIPKEQKYSF  LQNPQTSLCF
SESIPTPSNR  EETQQKSNLE  LLRISLLLIQ  SWLEPVQFLR  SVFANSLVYG              ASDSNVYDLL
KDLE  (SEQ ID NO: 1)
```

Please replace the paragraph beginning at page 24, line 16 with the following rewritten paragraph:

```
  1                                                    GAGGACTTAAATTAAATA
        Met Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr Gly    17
   19 ATG ATC CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG GGA

        Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn Asp    34
   70 CAA ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC GAC

        Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp Met    51
  121 GAT GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT ATG

        Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu Gly    68
  172 GAT AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG GGC

        Ser Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala His    85
  223 TCC ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA CAC

        Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala Tyr   102
  274 AGA TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG TAT

        Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser Leu   119
  325 ATT CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG CTG

        Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln Gln   136
  376 TGC TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG CAG

        Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser Trp   153
  427 AAA TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC TGG

        Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val Tyr   170
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478 TTG GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT TAT
    Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Stop      185
529 GGG GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC GAA TAA   (SEQ ID NO : 2)
```

Please replace the paragraph beginning at page 25, line 5 with the following rewritten paragraph:

```
MEIQTLMGRL EDGSPRTGQI FKQTYSKFDT NSHNDDALLK NYGLLYCFRK
DMDKVETFLR IVQCRSVEGS TIPLSRLFDN ASLRAHRLHQ LAFDTYQEFE
EAYIPKEQKY SFLQNPQTSL CFSESIPTPS NREETQQKSN LELLRISLLL
IQSWLEPVQF LRSVFANSLV YGASDSNVYD LLKDL (SEQ ID NO : 3)
```

Please replace the paragraph beginning at page 25, line 13 with the following rewritten paragraph:

```
  1                                          GAGGACTTAAATTAAATA
    Met Glu Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr   17
 19 ATG GAA ATC CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG
    Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn   34
 70 GGA CAA ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC
    Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp   51
121 GAC GAT GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT
    Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu   68
172 ATG GAT AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG
    Gly Ser Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala   85
223 GGC TCC ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA
    His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala   102
274 CAC AGA TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG
    Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser   119
325 TAT ATT CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG
    Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln   136
376 CTG TGC TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG
    Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser   153
427 CAG AAA TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC
    Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val   170
478 TGG TTG GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT
    Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Stop      185
529 TAT GGG GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC TAA   (SEQ ID NO : 4)
```

Please replace the paragraph beginning at page 25, line 54 with the following rewritten paragraph:

```
MQTLMGRLED   GSPRTGQIFK   QTYSKFDTNS   HNDDALLKNY   GLLYCFRKDM   DKVETFLRIV

QCRSVEGSTI   PLSRLFDNAS   LRAHRLHQLA   FDTYQEFEEA   YIPKEQKYSF   LQNPQTSLCF

SESIPTPSNR   EETQQKSNLE   LLRISLLLIQ   SWLEPVQFLR   SVFANSLVYG   ASDSNVYDLL

KDLE  (SEQ ID NO : 5)
```

Please replace the paragraph beginning at page 26, line 4 with the following rewritten paragraph:

```
 1                                                    GAGGACTTAAATTAAATA
       Met  Gln  Thr  Leu  Met  Gly  Arg  Leu  Glu  Asp  Gly  Ser  Pro  Arg  Thr  Gly  Gln      17
    19 ATG  CAG  ACC  TTA  ATG  GGC  CGC  CTG  GAA  GAC  GGT  AGC  CCG  CGG  ACG  GGA  CAA

       Ile  Phe  Lys  Gln  Thr  Tyr  Ser  Lys  Phe  Asp  Thr  Asn  Ser  His  Asn  Asp  Asp      34
    70 ATT  TTC  AAA  CAG  ACC  TAT  AGT  AAA  TTT  GAT  ACG  AAC  AGC  CAT  AAC  GAC  GAT

       Ala  Leu  Leu  Lys  Asn  Tyr  Gly  Leu  Leu  Tyr  Cys  Phe  Arg  Lys  Asp  Met  Asp      51
   121 GCT  CTA  CTG  AAA  AAC  TAT  GGT  CTG  CTC  TAC  TGC  TTC  CGC  AAG  GAT  ATG  GAT

       Lys  Val  Glu  Thr  Phe  Leu  Arg  Ile  Val  Gln  Cys  Arg  Ser  Val  Glu  Gly  Ser      68
   172 AAA  GTT  GAA  ACC  TTT  CTG  CGC  ATA  GTG  CAG  TGT  CGA  TCT  GTG  GAG  GGC  TCC

       Thr  Ile  Pro  Leu  Ser  Arg  Leu  Phe  Asp  Asn  Ala  Ser  Leu  Arg  Ala  His  Arg      85
   223 ACT  ATT  CCT  CTG  TCC  CGC  TTG  TTC  GAC  AAT  GCC  TCA  TTA  CGT  GCA  CAC  AGA

       Leu  His  Gln  Leu  Ala  Phe  Asp  Thr  Tyr  Gln  Glu  Phe  Glu  Glu  Ala  Tyr  Ile     102
   274 TTG  CAT  CAG  CTT  GCC  TTT  GAT  ACG  TAC  CAG  GAG  TTT  GAA  GAA  GCG  TAT  ATT

       Pro  Lys  Glu  Gln  Lys  Tyr  Ser  Phe  Leu  Gln  Asn  Pro  Gln  Thr  Ser  Leu  Cys     119
   325 CCG  AAG  GAG  CAA  AAA  TAC  TCT  TTT  CTG  CAA  AAT  CCG  CAG  ACC  TCG  CTG  TGC

       Phe  Ser  Glu  Ser  Ile  Pro  Thr  Pro  Ser  Asn  Arg  Glu  Glu  Thr  Gln  Gln  Lys     136
   376 TTC  AGT  GAA  AGC  ATT  CCG  ACT  CCA  TCG  AAC  CGT  GAG  GAA  ACA  CAG  CAG  AAA

       Ser  Asn  Leu  Glu  Leu  Leu  Arg  Ile  Ser  Leu  Leu  Leu  Ile  Gln  Ser  Trp  Leu     153
   427 TCC  AAT  CTG  GAA  CTG  CTT  CGT  ATC  AGC  TTA  CTG  CTC  ATC  CAA  AGC  TGG  TTG

       Glu  Pro  Val  Gln  Phe  Leu  Arg  Ser  Val  Phe  Ala  Asn  Ser  Leu  Val  Tyr  Gly     170
   478 GAA  CCC  GTC  CAA  TTC  CTT  CGT  TCA  GTG  TTT  GCG  AAT  AGT  CTG  GTT  TAT  GGG

       Ala  Ser  Asp  Ser  Asn  Val  Tyr  Asp  Leu  Leu  Lys  Asp  Leu  Glu  Stop           184
   529 GCA  AGT  GAC  TCT  AAC  GTC  TAT  GAT  CTG  CTG  AAA  GAT  CTC  GAA  TAA  (SEQ ID NO : 6)
```

Please replace the paragraph beginning at page 26, line 45 with the following rewritten paragraph:

```
MCIQTLMGRL EDGSPRTGQI FKQTYSKFDT NSHNDDALLK NYGLLYCFRK
DMDKVETFLR IVQCRSVEGS TIPLSRLFDN ASLRAHRLHQ LAFDTYQEFE
EAYIPKEQKY SFLQNPQTSL CFSESIPTPS NREETQQKSN LELLRISLLL
IQSWLEPVQF LRSVFANSLV YGASDSNVYD LLKDLEC     (SEQ ID NO : 7)
```

Please replace the paragraph beginning at page 26, line 54 with the following rewritten paragraph:

```
  1                                        GAGGACTTAAATTAAATA
      Met Cys Ile Gln Thr Leu Met Gly Arg Leu Glu Asp Gly Ser Pro Arg Thr     17
   19 ATG TGT ATC CAG ACC TTA ATG GGC CGC CTG GAA GAC GGT AGC CCG CGG ACG
      Gly Gln Ile Phe Lys Gln Thr Tyr Ser Lys Phe Asp Thr Asn Ser His Asn     34
   70 GGA CAA ATT TTC AAA CAG ACC TAT AGT AAA TTT GAT ACG AAC AGC CAT AAC
      Asp Asp Ala Leu Leu Lys Asn Tyr Gly Leu Leu Tyr Cys Phe Arg Lys Asp     51
  121 GAC GAT GCT CTA CTG AAA AAC TAT GGT CTG CTC TAC TGC TTC CGC AAG GAT
      Met Asp Lys Val Glu Thr Phe Leu Arg Ile Val Gln Cys Arg Ser Val Glu     68
  172 ATG GAT AAA GTT GAA ACC TTT CTG CGC ATA GTG CAG TGT CGA TCT GTG GAG
      Gly Ser Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Ser Leu Arg Ala     85
  223 GGC TCC ACT ATT CCT CTG TCC CGC TTG TTC GAC AAT GCC TCA TTA CGT GCA
      His Arg Leu His Gln Leu Ala Phe Asp Thr Tyr Gln Glu Phe Glu Glu Ala    102
  274 CAC AGA TTG CAT CAG CTT GCC TTT GAT ACG TAC CAG GAG TTT GAA GAA GCG
      Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro Gln Thr Ser    119
  325 TAT ATT CCG AAG GAG CAA AAA TAC TCT TTT CTG CAA AAT CCG CAG ACC TCG
      Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Thr Gln    136
  376 CTG TGC TTC AGT GAA AGC ATT CCG ACT CCA TCG AAC CGT GAG GAA ACA CAG
      Gln Lys Ser Asn Leu Glu Leu Leu Arg Ile Ser Leu Leu Leu Ile Gln Ser    153
  427 CAG AAA TCC AAT CTG GAA CTG CTT CGT ATC AGC TTA CTG CTC ATC CAA AGC
      Trp Leu Glu Pro Val Gln Phe Leu Arg Ser Val Phe Ala Asn Ser Leu Val    170
  478 TGG TTG GAA CCC GTC CAA TTC CTT CGT TCA GTG TTT GCG AAT AGT CTG GTT
      Tyr Gly Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Cys    187
  529 TAT GGG GCA AGT GAC TCT AAC GTC TAT GAT CTG CTG AAA GAT CTC GAA TGT
      Stop                                                                   187
  580 TAA   (SEQ ID NO : 8)
```

Please insert the attached Abstract as the last page of the specification.